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Women's Health

Investor Day

29.11.2021

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Agenda

Donesta

Jean-Michel Foidart
(Co-founder of Mithra)
Graham Dixon *(CSO)*
Carolyn Myers
(Principal at BioEnsemble)



BCI, Diversification of Mithra's pipeline beyond Estetrol

Graham Dixon *(CSO)*

Update on Nextstellis®

Donald Pearl
(Executive VP, Specialty Brands at Mayne Pharma)

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Donesta®

Donesta – 1st part

Prof. Jean-Michel Foidart
(Co-founder of Mithra)

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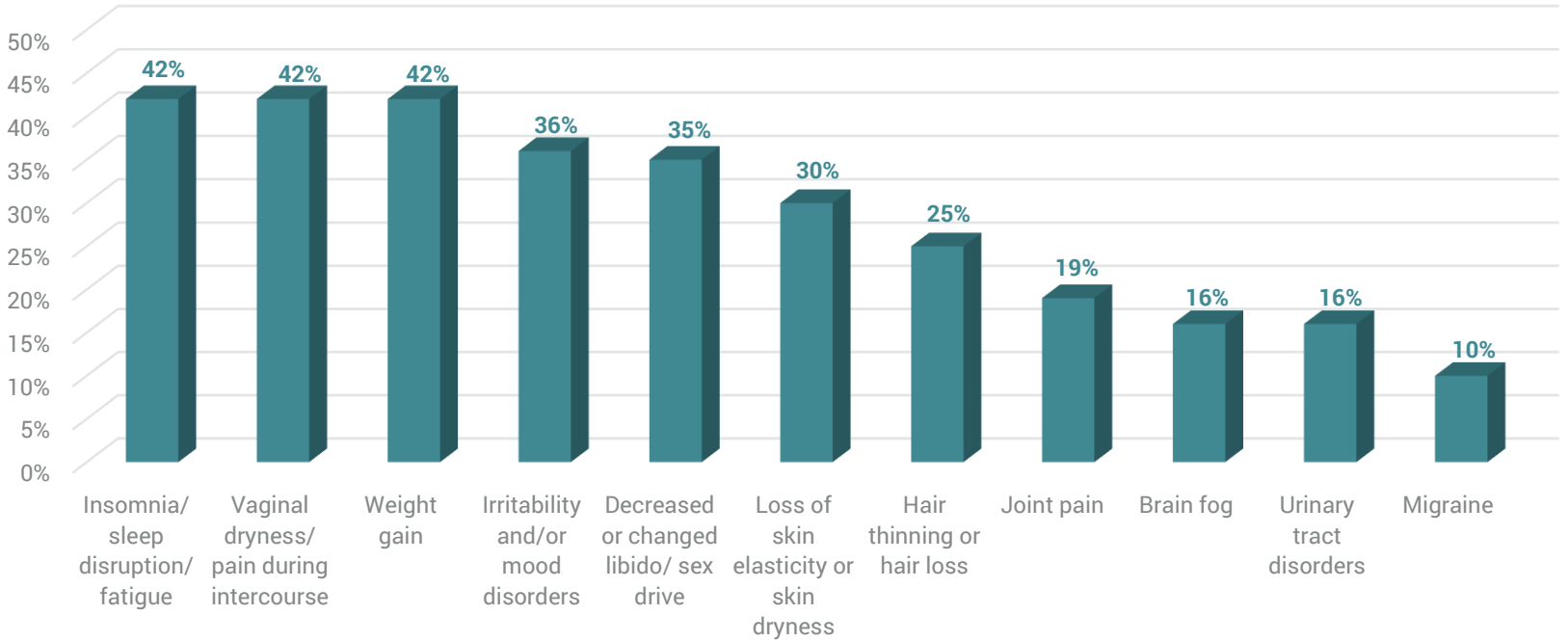
What is menopause ?

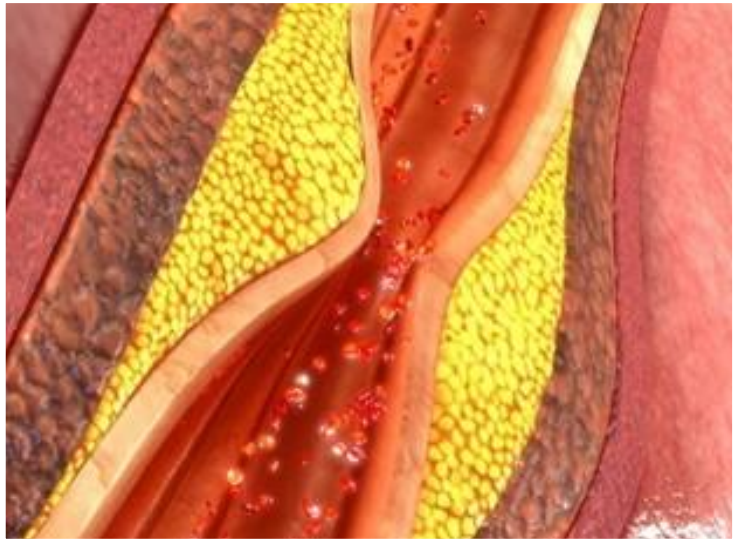
- Menopause is a natural part of the ageing process when menstrual cycles permanently cease activity due to the loss of ovarian follicular function due to aging, **decreasing the amount of hormones** the body makes, **particularly estrogen** and progesterone.
- Ultimately, all women who reach a certain age – average 51 – will reach menopause. Of these, **75% will get one or multiple troublesome symptoms** that deteriorate their quality of life.

Beyond VMS symptoms, women experience a number of other menopause-related symptoms



Source: IQVIA quantitative market research, 2021

Postmenopausal obesity and CV diseases



- The absence of estrogens is an important obesity-triggering factor. It develops in **65% of American women** after they reach **age 40 years** and is present in **74% in women over age 60**.

- Estrogens deficiency exacerbates **metabolic dysfunction** predisposing to **Diabetes type 2**, the **metabolic syndrome**, **atherosclerosis** and **cardiovascular diseases**, the leading cause of death in postmenopausal women.

Menopause in figures

There are **significant unmet needs** in the treatment of menopause symptoms primarily **due to the safety concerns** associated with use of **existing hormones**.

Only 1 in 10 women with menopause take Hormone Therapy (HT), despite HT being the most effective therapy for the large majority of women.

Women spend **+/- 40% of their life** time in menopause.
About 25 million women pass through menopause **each year** (1).

By 2030, the world population of menopausal and postmenopausal women is projected to **increase by over 1.2 billion.** Blockbuster market with around **47 million new entrants each year** globally (2).

(1) National Center for Biotechnology Information (NCBI)
(2) Maturitas. The demography of menopause. 1996 Mar;23(2):113-27. doi: 10.1016/0378-5122(95)00968-x. Viewed September 21, 2021. https://pubmed.ncbi.nlm.nih.gov/8735350/

Existing and upcoming treatments

- Hormone therapy (HT)

Estro-progestative combination	Estrogen only

- Non-hormonal therapy (NHT)

CNS* derived solutions (NK3)	Anti-depressants	Anti-epileptics

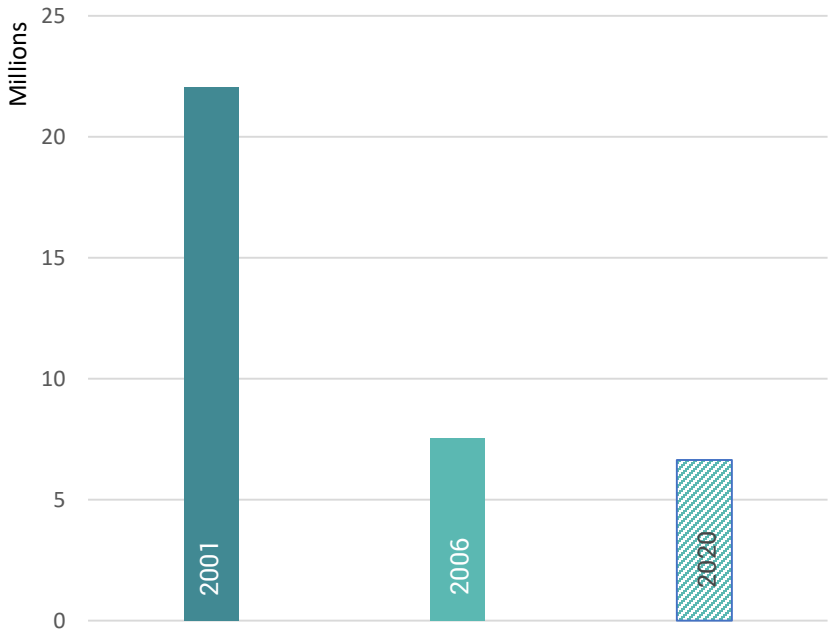
*CNS: Central Nervous System

Hormone Therapy (HT)

- Treatment recommended to **relieve common symptoms of menopause** and to address **long-term biological changes** that result from declining levels of the natural hormones (estrogen and progesterone) during and after menopause.
- HT also helps **to balance estrogen and progesterone** in women around the time of menopause.
- History of HT started **in the 1960s**; first clinical trials on HT and chronic postmenopausal conditions started **in the late 1990s**.
- **Collapsing** of HT's use worldwide after the announcement of the first results of the **Women's Health Initiative (WHI) in 2002**, which indicated that HT could have more detrimental than beneficial effects.

Influence of WHI report on HT use – HT use collapsed following publication of initial results

Number of patients with HT in 2001- 2006 - 2020



Source: IQVIA primary and secondary market research, 2021

In 2001, 22 million women treated with HT for menopause symptoms, currently only 7 million despite revised WHI 2006 HT recommendations

- Following publication of WHI report; more than **85% of women in the USA** stopped taking HT and **63% in Europe** due to concerns of risk of breast cancer and cardiovascular disease.
- **In 2006, WHI** updated analysis confirmed no increased risk of breast cancer with estrogen-alone HT, however **the market has not recovered**.
- There have been **few innovations** to treat menopause symptoms since publishing of the WHI.

Broad Stakeholder support for HT use in menopause

NAMS Conclusion

> **Hormone therapy is the most effective treatment for VMS and GSM and has been shown to prevent bone loss and fracture. Benefits are most likely to outweigh risks for symptomatic women who initiate HT when aged younger than 60 years or who are within 10 years of menopause onset.**

The 2017 hormone therapy position statement of The North American Menopause Society

Thought Leaders View

> **Late analysis of WHI data shows that if you look only at women between the ages of 50 and 59, when most women use it and need it, there are clear benefits of HT. These women had fewer cancers, fractures and deaths from any cause compared with the women taking placebo.**

Dr Ginni Mansberg, KOL.

WHI Final Report:

> **Among postmenopausal women, hormone therapy with CEE alone for a median of 7.2 years was not associated with risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years.**

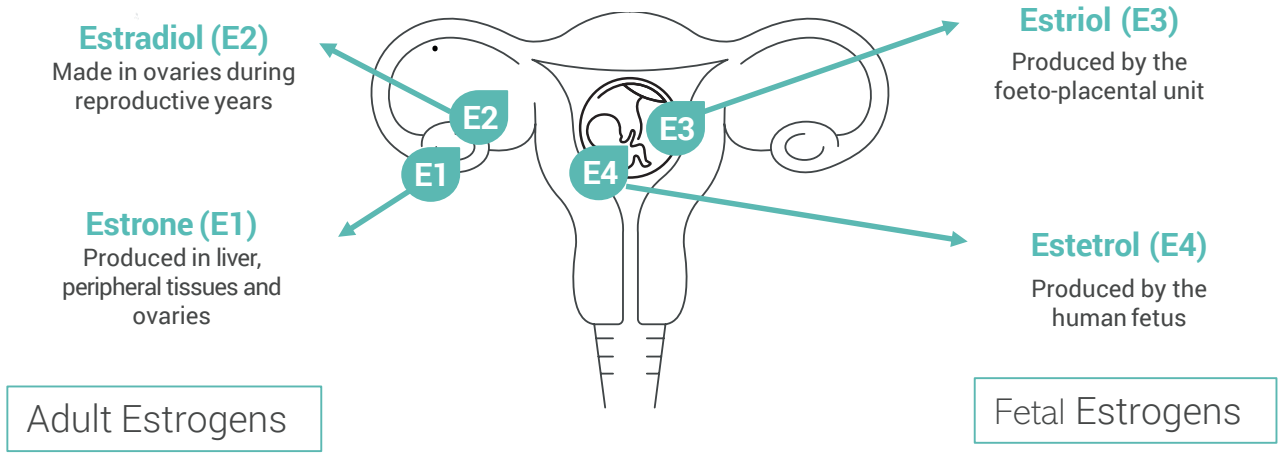
Conclusion of a new release of data from the WHI study[1]

Donesta® could disrupt the menopause market being first native Hormone Therapy. Currently available data suggest an improved benefit/risk profile compared to other kind of therapies.

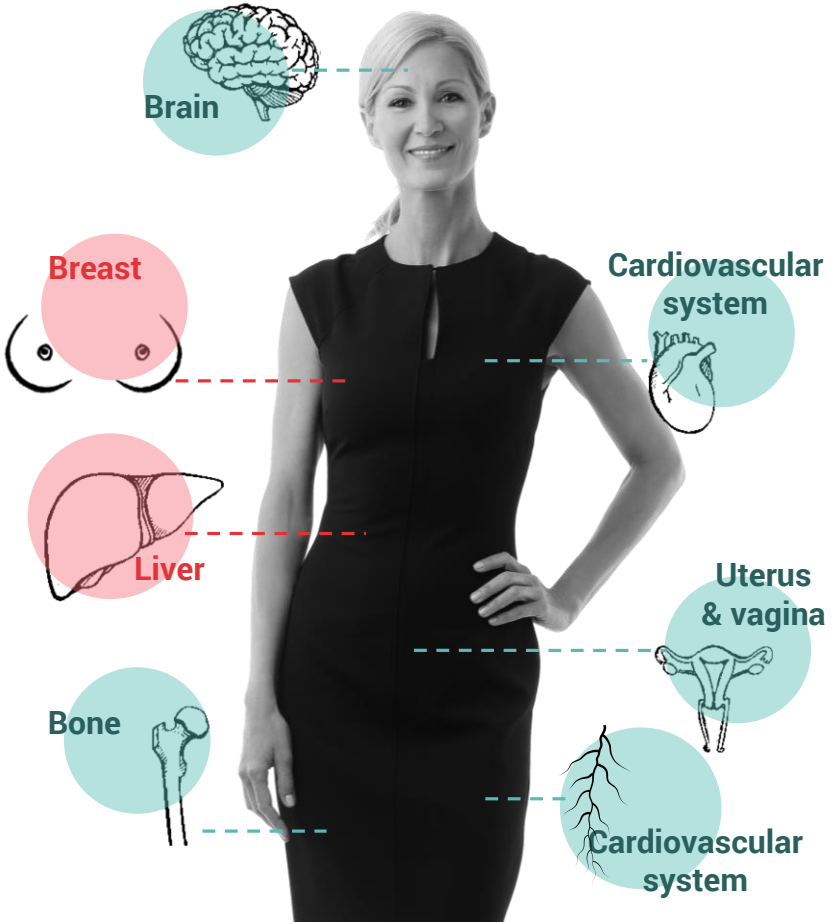
1 Manson JE. JAMA 2017; 318:927-38.

Donesta® - The native generation of hormone therapy based on Estetrol

The FDA and EMA recognized that Estetrol (E4) is a New Chemical Entity, an early life estrogen **distinct from existing conventional adult estrogens marketed.** Both institutions have recently approved Mithra's E4 Combined Oral Contraceptive, providing **a clear path forward for approval for Donesta®.**



Impact of classical estrogens



Positive actions

- **Brain**: ovulation inhibition / VMS[1] relief / Neuroprotection
- **Uterus**: maintenance of uterovaginal trophicity
- **Bone**: prevention of bone demineralization
- **Vagina**: maintenance of uterovaginal trophicity
- **Cardiovascular system**: cardioprotective effects

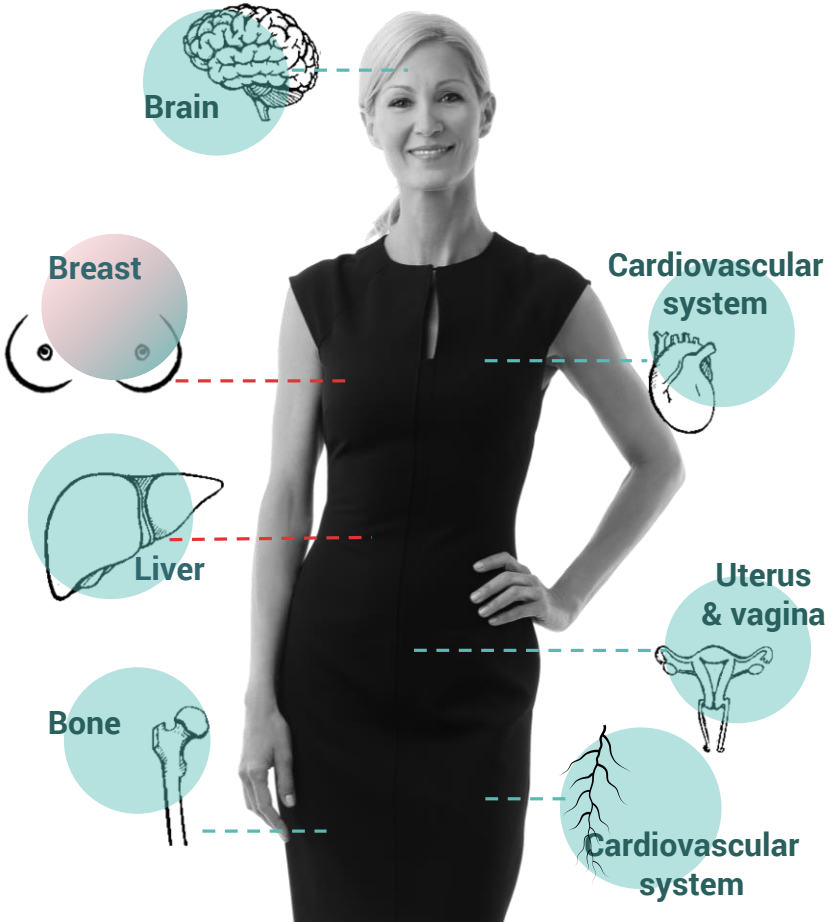
Negative actions

- **Breast**: stimulation - risk of cancer
- **Liver**: increase in
  - SHBG[2] synthesis.
  - Synthesis of coagulation factors (associated to VTE risk).
  - Lipid production (associated to coronary heart diseases).

Deroo BJ, Korach KS. J Clin Invest. 2006 | Thomas C, Gustafsson JA. Nat Rev Cancer 2011 | Arnal JF. et al. Physiol Rev 2017 |Valera MC. et al. Pharmacol Ther 2018 | - Mauvais-Jarvis F et al. Endocr Rev 2013)

(1) Vasomotor symptoms; (2) Sex Hormone Binding Globulin

E4 presents a favorable safety profile



- Similar to other estrogens, E4 has also a beneficial and positive impact on the cardiovascular system, brain, bone and endometrium
- Unlike other estrogens, E4 has a limited impact on the liver and the breast

Breast: mixed activity on breast cell proliferation, migration and invasion[1], limited impact on breast at therapeutic dose

Liver:

- minimal impact on SHBG[2] synthesis
- minimal impact on synthesis of coagulation factors (lower risk of VTE)
- limited lipid impact (including TGs[3])

(1) In presence of Estradiol (E2); (2) Sex Hormone Binding Globulin; (3) Triglycerides

Visser et al. Climacteric 2008 | Mawet et al. Eur J Contracept Reprod Health Care 2015 | Gérard et al. J Endocrinol 2015 | Abot et al. EMBO Mol Med 2014 | Coelingh Bennink et al. Climacteric 2008 | Heegaard et al. Climacteric 2008 | Holinka et al. Biol Reprod. 1980 | Holinka et al. Climacteric 2008 | Pluchino et al. J Steroid Biochem Mol Biol 2014 | Tskitishvili et al. Exp Neurol 2014 | Guivarc'h et al. J Am Heart Assoc 2018 | Kluft et al. Contraception 2017 | Douxfils et al. Contraception 2020 | Klipping et al. Contraception 2021

Donesta – 2nd part

Graham Dixon
(Chief Scientific Officer)

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E4 is safe for the aquatic environment

EE (ethynyl estradiol)

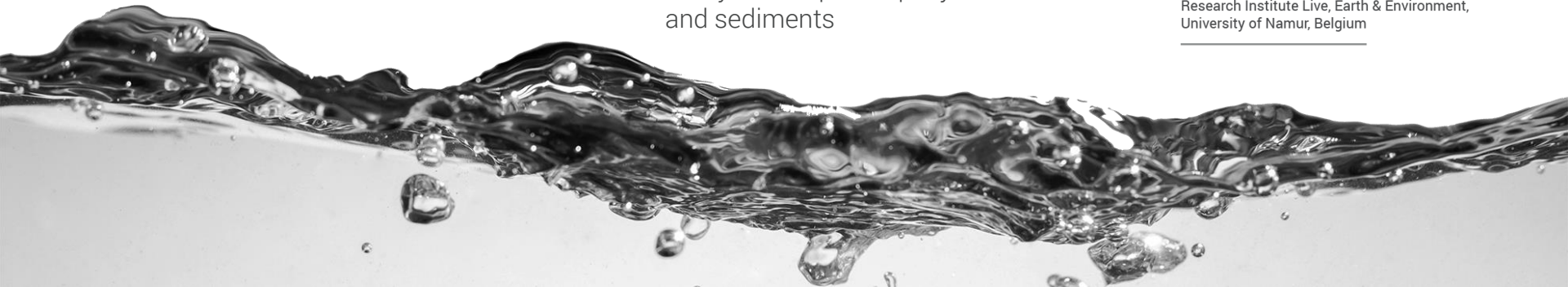
- 97% of current marketed Combined Oral Contraceptives are based on EE
- Known as a major Endocrine Disrupting Chemical

E4 (Estetrol)

- Insignificant endocrine disruptor effects, whether in aquatic organisms or organisms living in the sediment
- Amount of biologically active E4 released in the wastewaters after human use expected to be minimal
- Does not accumulate in living organisms
- Likely to dissipate rapidly from water and sediments

> **“All biotests carried out show without ambiguity that the endocrine disruptor effects of Estetrol are insignificant in comparison with those observed for natural or synthetic estrogens, whether in aquatic organisms or organisms living in the sediment.”**

Prof. Patrick Kestemont, President of the Research Institute Live, Earth & Environment, University of Namur, Belgium



Phase II: dose-finding study results

- All E4 doses studied improved genitourinary syndrome of menopause (GSM)/Vulvovaginal atrophy (VVA)

2.5 mg	5 mg	10 mg	15 mg

- E4 doses of 15 mg :
  - Significantly reduced the frequency and severity of VMS
  - Positively influenced bone turnover
  - Did not increase triglyceride levels
  - Increased HDL (good cholesterol)
  - Improved glucose tolerance
  - Had no effects on coagulation parameters
- No apparent safety concerns regarding endometrial safety and adverse events.

➔ E4 was well-tolerated

NAMS 2019
Gaspard et al. Menopause 2020

E4 has potential to address additional symptoms of ageing

Patients will benefit from long-term administration of natural estrogens to be more healthy (keep skin structure intact and bones stronger, lower risk of diabetes)

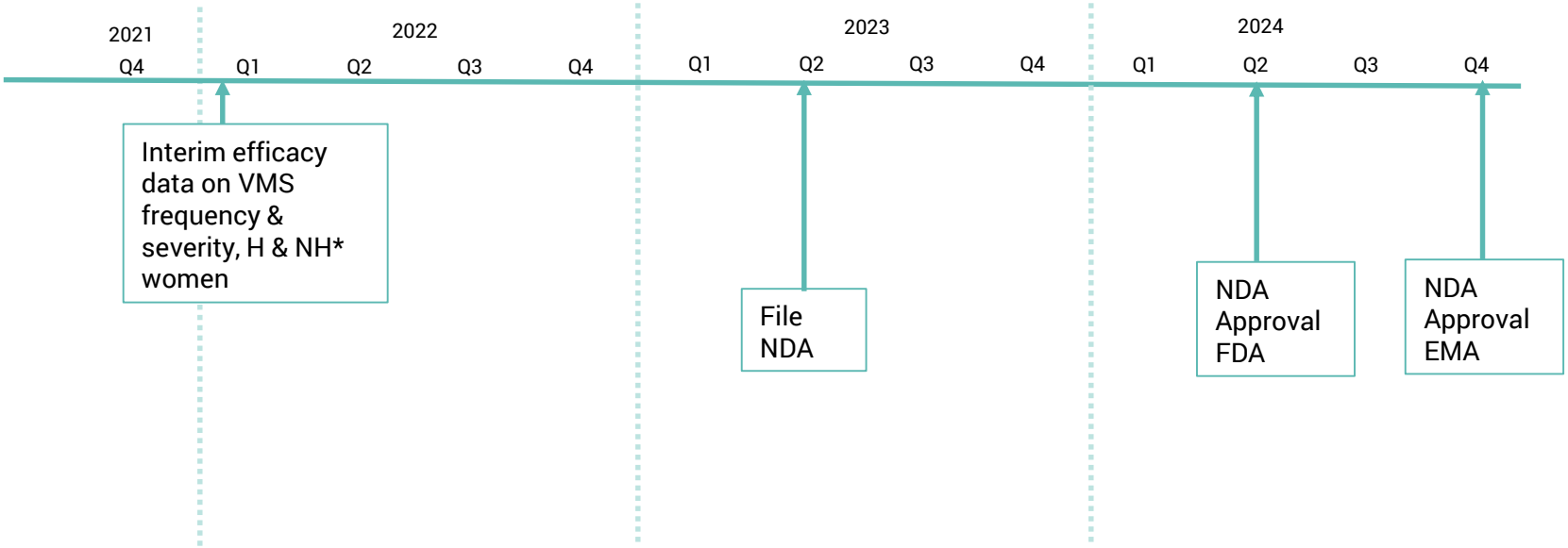
- **E4, in addition, has unique beneficial properties for aging prevention/protection** (Unique Benefits of E4 versus deleterious activities of E2 and other estrogens)
- **Estrogen deprivation** is one the major factor responsible for delayed healing in elderly humans.
- E4 prevents **Western diet-induced obesity, steatosis and atheroma**
- E4 is n**europrotective**, promotes neuron proliferation, neural angiogenesis and myelin deposition

Donesta® has the potential to target menopausal symptoms beyond VMS

Clinical Phase	Primary Endpoint	Secondary Endpoint
Phase 3	E4 effect on reducing Vaso-Motor Symptom frequency / severity, H & NH* women	Effect on lipids, glucose metabolism, hemostasis parameters, breast density endometrial safety, health-related quality of life, treatment satisfaction and vulvar and Vulvo-vaginal atrophy
Phase 3	E4 effect on improvement of Vulvo-Vaginal Atrophy	Effect on various aspects of Female Sexual and Urogenital Functions
Phase 2	Effect of E4 on skin texture, quality and appearance	Effect of E4 on quality of life and various skin-related endpoints
Phase 2	Effect of E4 on hair texture, quality and appearance	Effect of E4 on quality of life and various hair-related endpoints

* Hysterectomized and non-hysterectomized

Donesta® : expected timeline



* Hysterectomized and non-hysterectomized

Donesta – 3rd part

Carolyn Myers
(Principal, BioEnsemble)

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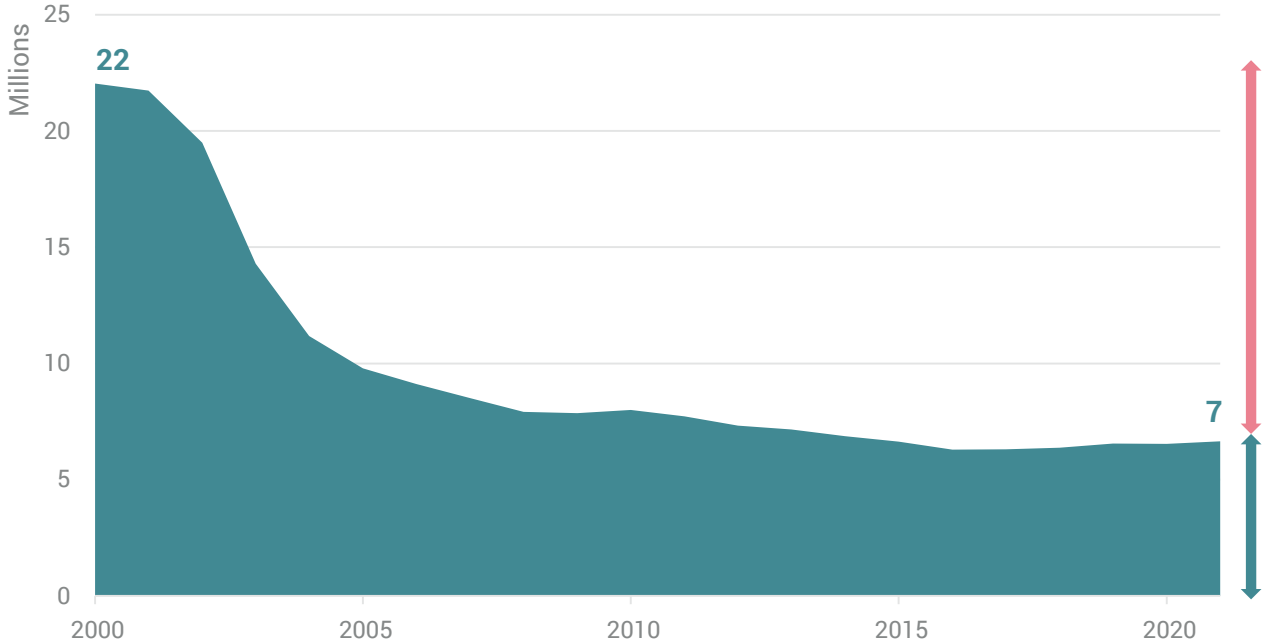
Global blockbuster opportunity for Donesta

Evolution of menopausal patients treated in US & EU since 2000



22 million women on HT in 2001

15 million women lost from current HT market

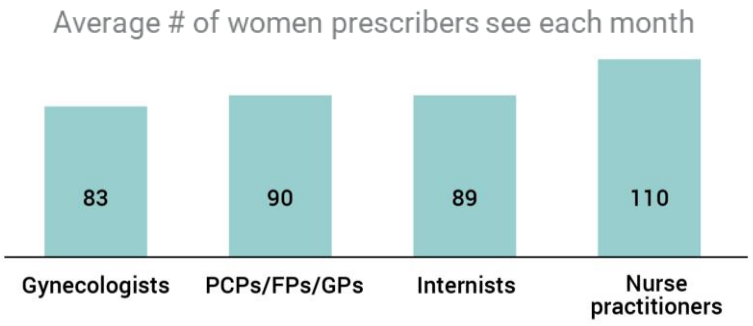
By 2020 on 6.7 million women on HT

Source: IQVIA primary and secondary market research, 2021

US Quantitative Market Research Survey

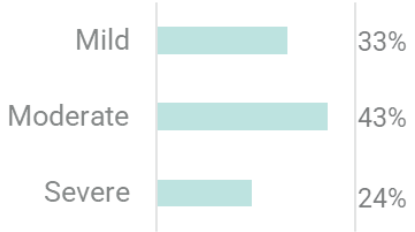
PHYSICIAN SURVEY

Prescriber cohort		Target
Gynecologists	High/Mid income	44
	Low income	6
Primary care physician's, internists, etc.	High/Mid income	59
	Low income	11
Total		**120**



WOMEN SURVEY

Surveyed 500 women with mild/moderate/severe symptoms

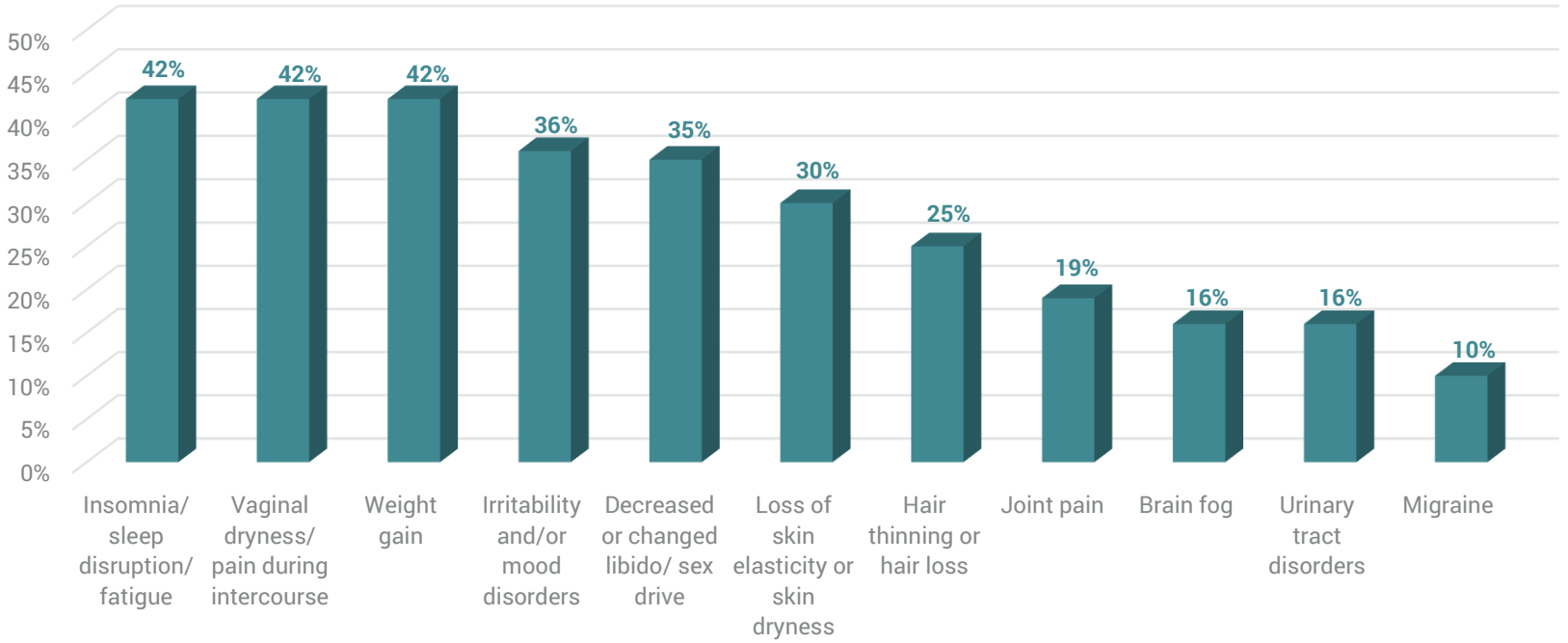


Cohorts included:

Never taken treatment	20%
Taking FDA approved hormones	30%
Taking compounded hormones	20%
Taking OTC products	20%
Other	10%

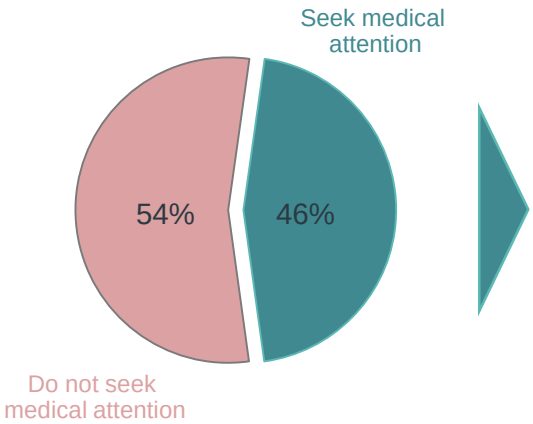
Source: IQVIA primary and secondary market research, 2021

Beyond VMS symptoms, women experience a number of other menopause-related symptoms



Source: IQVIA quantitative market research, 2021

Of the 46% of women who seek treatment, most take FDA approved hormones



Treatment option	Observations of Those Who See Physicians	% of women
FDA Approved Hormones	• Women with moderate to severe symptoms more inclined to take hormones	37%
Other FDA Approved Products	• Women take these alternatives to manage bothersome symptoms and to reduce concern of breast cancer risk	24%
Compounded Hormones	• Many women believe compounded hormones are safer and tailored to their individual needs	11%
OTC	• Women take when menopause symptoms are mild	11%
No Treatment	• Many women decide not to take treatment as they have concerns about risk of breast cancer	17%

Source: IQVIA quantitative market research, 2021

Positive response to blinded Donesta® product profile

Physicians

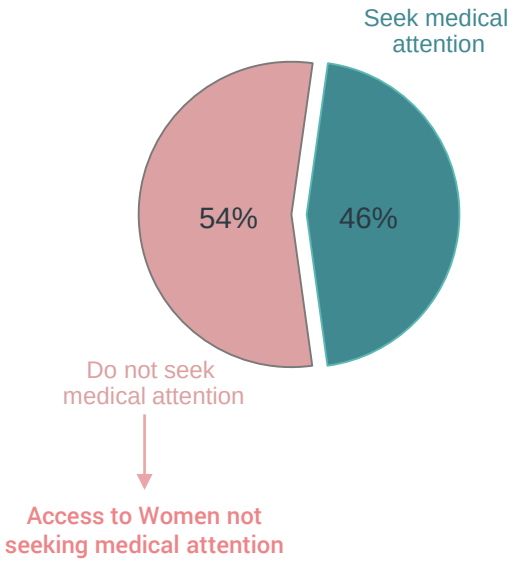
- Perceived very positively as a safe estrogen
  - Reduced breast cancer risk
  - No drug-drug interactions
  - Reduced risk of thrombotic disease
  - Natural
  - Treats multiple symptoms of menopause

Women

- Significant number of women surveyed would consider this option as it has a safe profile
- Like that it is natural
- Potential to treat many symptoms of menopause
  - Reduce hot flashes/night sweats
  - Improve sleep
  - Improve libido
  - Reduce hair loss
  - Maintain skin elasticity

Source: IQVIA quantitative market research, 2021

Significant opportunity to capture share from current treated population and from women not taking treatment



High potential of 15 million untreated women

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On average significant potential to take share from existing segments

Source: IQVIA quantitative market research, 2021

Conclusion

- There are significant unmet needs in the treatment of menopause symptoms primarily due to the safety concerns associated with use of hormones.
- **Only 1 in 10 women** with menopause **take Hormone Therapy** (HT), despite HT being the most effective therapy for the large majority of women.
- **Women spend +/- 40% of their lifetime in menopause**. National Center for Biotechnology Information (NCBI) stated that about 25 million women pass through menopause each year.
- By 2030, the world population of menopausal and postmenopausal women is projected to increase to 1.2 billion. (1) - Blockbuster market with around 47 million new entrants each year globally (1).

Conclusion

- Estrogen-based HT proven to be most effective, but because women and physicians still perceive it as unsafe, millions of women are on suboptimal treatment.
- Market lacks new innovative HT solutions to treat menopausal symptoms.
- Donesta® should disrupt the menopause market being first native hormone therapy (HT) for menopausal women:
    - Improved benefit/risk profile compared to other estrogens;
    - Potential to address the broad range menopause symptoms;
    - Oral once per day;
    - Environmentally friendly;
    - Potential for treating symptoms through the duration of menopause.

Q&A

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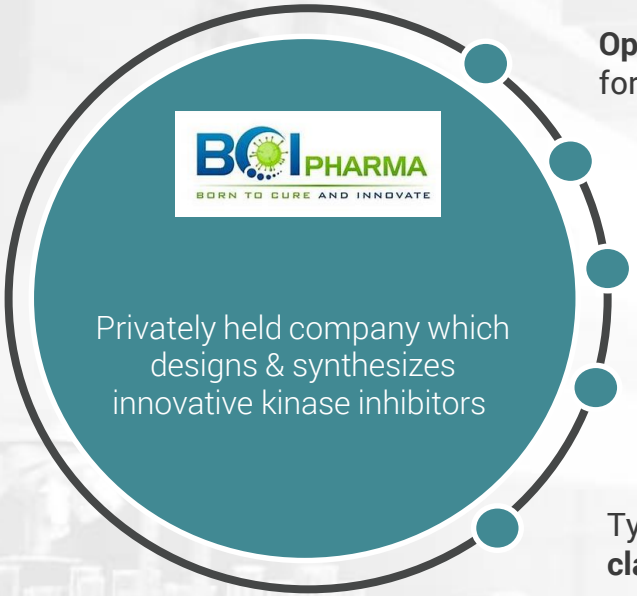
BCI

Diversification of Mithra's pipeline beyond Estetrol

Executive Summary



Option to acquire 2 patents covering CSF1R inhibitor series for EUR 2.25 million upfront on execution of option

Acquisition expands **Mithra's R&D asset-based pipeline** and builds on Mithra's strength as biotech dedicating to innovation in Women's Health

CSF1R is a tyrosine kinase and represents an exciting new class of immune-modulatory drugs with established clinical tolerability[1] and proven efficacy[2]

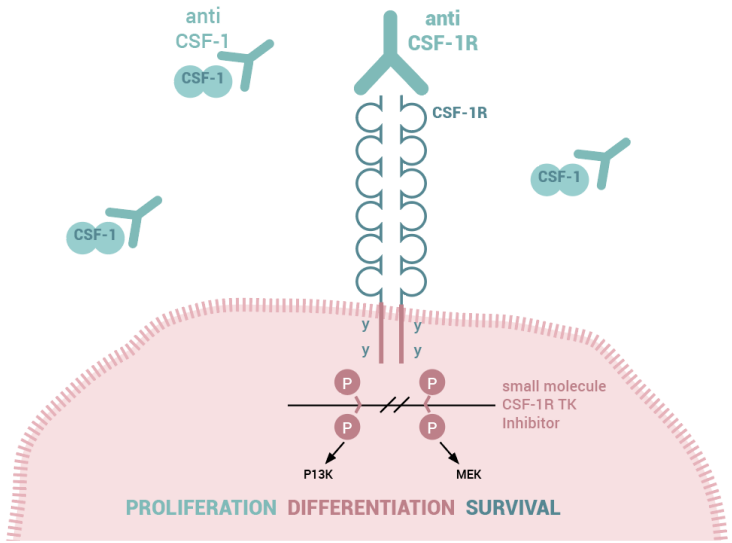
CSF1R receptor is involved in many **inflammatory processes** and is over expressed in many **pathologies including cancers and neurological disorders**

Tyrosine kinases are the third **fastest growing third level therapeutic class** in 2020, with a 17% increase in revenues to USD 40.3 billion[3]

Opportunity to generate potential additional Products and indications to diversify R&D pipeline beyond E4 in a fast growing market

(1) Cannarile et al. Journal for ImmunoTherapy of Cancer (2017) 5:53
(2) Monsestime et al. Drugs in R&D (2020) 20:189–195
(3) IQVIA FY 2020

Colony Simulating Factor 1 Receptor (CSF1R)



Targeting CSF1R is a demonstrated and attractive strategy in immune-modulatory treatments[1]

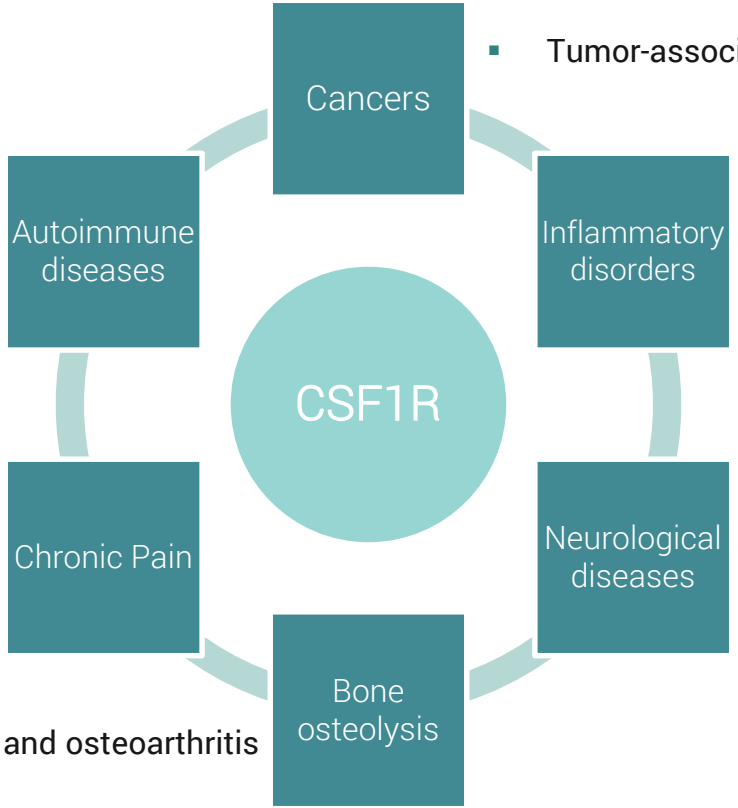
CSF1R signaling pathway is **crucial** for the differentiation, proliferation and survival of cells from the immune system [1]

Dysregulation of the pathway is **associated with many disorders** having immune and inflammatory components [2]

The presence of **CSF1R macrophages** in the tumor correlates with poor prognosis in several cancers [1,3,4]

(1) Cannarile et al. Journal for ImmunoTherapy of Cancer (2017) 5:53
(2) Blood, **2012**, *119*, 1810
(3) Pedersen MB, Danielsen AV, Hamilton-Dutoit SJ, Bendix K, Norgaard P, Moller MB, Steiniche T, d'Amore F. High intratumoral macrophage content is an adverse prognostic feature in anaplastic large cell lymphoma. Histopathology. 2014;65:490–500
(4) Zhang QW, Liu L, Gong CY, Shi HS, Zeng YH, Wang XZ, Zhao YW, Wei YQ. Prognostic significance of tumor-associated macrophages in solid tumor: a meta-analysis of the literature. PLoS One. 2012;7:e50946

Broad therapeutic potential of CSF1R inhibitors



- Tumor-associated macrophage

- Rheumatoid arthritis
- Inflammatory bowel diseases – Crohn's disease
- Inflammatory pulmonary diseases
- Endometriosis

- Epilepsy
- Alzheimer's disease
- Multiple sclerosis
- Charcot-Marie-Tooth disease
- Amyotrophic lateral sclerosis

- Osteoporosis and osteoarthritis

- Cancer-induced
- Chemotherapy-induced
- Diabetes-induced
- Nerve injury

- Psoriasis
- Systemic lupus erythematosus

Biomedecine&pharmacotherapy, 2018, 103, 662 ; JMedChem, 2018, 61, 5450 ; Trends Neurosci., 2016, 39, 378

Research plan and anticipated milestones

Initial focus for clinical development in female cancers and/or endometriosis

Potential to target orphan indications e.g. metastatic breast cancer (TNBC)

1. Study MYR301: Phase 3 evaluation of long-term dosing (144 weeks) of 2mg or 10mg bulevirtide as monotherapy. 2. Study MYR204: Phase 2b evaluation of finite-duration of therapy of 2mg or 10mg bulevirtide alone or in combination with pegylated interferon-alpha (48 weeks combination with interferon followed by 48 weeks of bulevirtide).

Rationale

- Expands Mithra's R&D pipeline and builds on Mithra's strength as biotech dedicating to innovation in Women's Health.
- CSF1R is a tyrosine kinase and represents an exciting new class of immune-modulatory drugs with established clinical tolerability[1] and proven efficacy[2]
- Tyrosine kinases were the third fastest growing therapeutic class in 2020, with a 17% increase in revenues to USD 40.3 billion[3]

Opportunity to generate potential additional indications to diversify R&D pipeline beyond E4 in a fast growing market

(1) Cannarile et al. Journal for ImmunoTherapy of Cancer (2017) 5:53; (2) Monsestime et al. Drugs in R&D (2020) 20:189–195; (3) IQVIA FY 2020;

Transaction details

- Option to acquire **2 patents** covering CSF1R inhibitor series for **EUR 2.25 million** upfront on execution of option
- BCI is conducting initial preclinical research and Mithra will trigger acquisition option upon demonstration of **product candidate criteria**
- Preclinical and Clinical Development to be entirely funded by Mithra up **to out-license to a third party**

Transaction will add another transformative element to the pipeline to further enhance Mithra's women's health business

(1) Cannarile et al. Journal for ImmunoTherapy of Cancer (2017) 5:53; (2) Monsestime et al. Drugs in R&D (2020) 20:189–195; (3) IQVIA FY 2020;

Q&A

Coffee break

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Nextstellis®

Update on US market

NEXTSTELLIS® launch continues to gain momentum

HCP engagement

- >50,000 interactions with healthcare providers (HCPs) including >5,000 promotional education lunches
- Sales team reached >6,000 HCPs and 70% of top prescriber targets
- NEXTSTELLIS® awareness amongst targeted HCPs is ~68% from a baseline of 2% at launch and ~48% have an intent to prescribe

Market access

- Commercial coverage[1]: 67% formulary access, 55% unrestricted
- Medicaid: 94% formulary access, 34% unrestricted

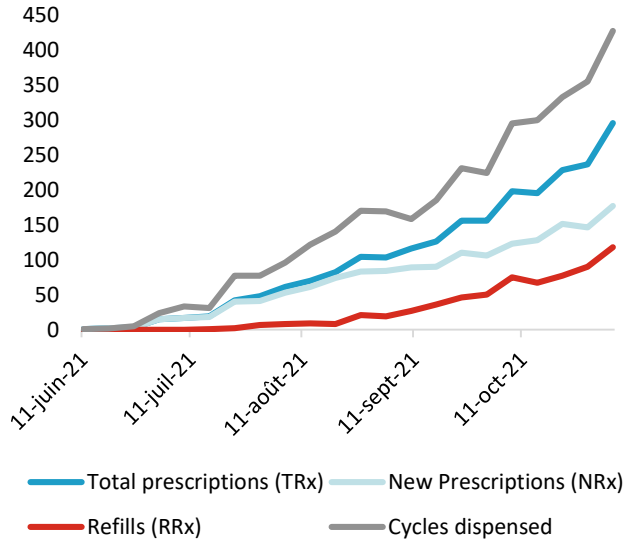
Underlying demand

- >850 NEXTSTELLIS® writers
- >7,000 TRx written
- >3,000 TRx dispensed and >5,000 cycles since launch

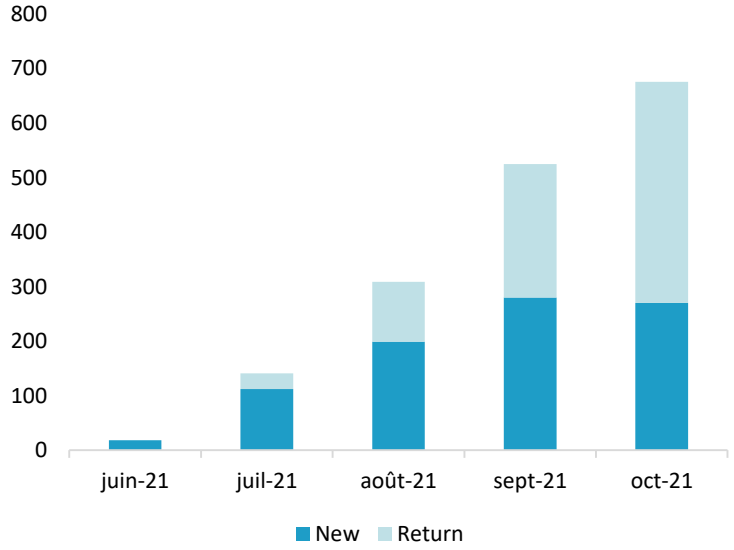
1. Health insurance coverage of patient lives

NEXTSTELLIS® key performance metrics

NEXTSTELLIS® weekly performance metrics



NEXTSTELLIS® writers



Source: IQVIA weekly prescription data, 5 November 2021

Q&A

Thank you for
your attention!

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Contact us

investorrelations@mithra.com

Rue St-Georges 5/7 - 4000 Liège
Tel : +32 (0)4 349 28 22
investors.mithra.com